Note: Performing your original search, ***toxicity benzethonium***, in PubMed will retrieve *13* citations.

1: Reg Anesth Pain Med. 1999 Mar-Apr;24(2):146-52. Related Articles, Links

ELSEVIER FULL-TEXT ARTICLE

Subarachnoid ketamine in swine--pathological findings after repeated doses: acute toxicity study.

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BACKGROUND AND OBJECTIVES: The purpose of this study was to investigate whether 5% ketamine with and without preservative, administered intrathecally to swine, produced a clinical anesthetic effect and caused direct subacute neurotoxicity. METHODS: Twenty pigs were used. Under general anesthesia, a subarachnoid catheter was placed at L5-L6 or L6-S1 spinal interspace. Five animals were used for initial clinical evaluation of the anesthetic effects of subarachnoid ketamine (12.5 and 25.0, and 500 mg). Two animals were excluded because of bloody taps, two served as controls (catheterization without drug administration), four received ketamine racemate (25.0 mg/d), four received ketamine racemate preservative free (25.0 mg/d), and three received benzethonium chloride, the ketamine excipient (0.05 mg/d). All drugs were administered for 7 days. The catheters were withdrawn at the end of the treatment period. After 35 days, the pigs were euthanized and the spinal cord removed and preserved for histopathologic study with hematoxilyn-eosin and luxol-fast blue myelin staining. Histopathologic effects were defined as absent/minimal, mild, or severe by a pathologist, unaware of group allocation, by evaluating the presence and intensity of peripheral and/or central chromatolysis, spongiosis, neuronal loss, perivascular neuroglia, neuronolysis, and myelin degeneration. RESULTS: All doses of ketamine produced immediate cutaneous anesthesia and motor block; benzethonium chloride did not. Histopathologic examination showed no neurotoxic effect of ketamine without preservative; ketamine with preservative showed a discrete neurotoxic effect, and the preservative alone produced a moderate neurotoxic effect. CONCLUSIONS: Clinically, in swine, subarachnoid ketamine without preservative is a safe and effective anesthetic and did not show significant neurotoxic effects. However, ketamine with preservative produces minimal changes, and benzethonium chloride alone produces moderate neurotoxic effects.

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Note: Performing your original search, ***benzethonium preservative***, in PubMed will retrieve *8* citations.

1: Br J Pharmacol. 2001 Oct;134(4):871-9. Related Articles, Links

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Ketamine and its preservative, benzethonium chloride, both inhibit human recombinant alpha7 and alpha4beta2 neuronal nicotinic acetylcholine receptors in Xenopus oocytes.

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1. Ketamine is a dissociative anaesthetic that is formulated as Ketalar, which contains the preservative benzethonium chloride (BCl). We have studied the effects of pure racemic ketamine, the preservative BCl and the Ketalar mixture on human neuronal nicotinic acetylcholine receptors (nAChRs) composed of the alpha7 subunit or alpha4 and beta2 subunits expressed in Xenopus laevis oocytes. 2. Ketamine inhibited responses to 1 mM acetylcholine (ACh) in both the human alpha7 and alpha4beta2 nAChRs, with IC(50) values of 20 and 50 microM respectively. Inhibition of the alpha7 nAChRs occurred within a clinically relevant concentration range, while inhibition of the alpha4beta2 nAChR was observed only at higher concentrations. The Ketalar formulation inhibited nAChR function more effectively than was expected given its ketamine concentration. The surprising increased inhibitory potency of Ketalar compared with pure ketamine appeared to be due to the activity of BCl, which inhibited both alpha7 (IC(50) value of 122 nM) and alpha4beta2 (IC(50) value of 49 nM) nAChRs at concentrations present in the clinical formulation of Ketalar. 3. Ketamine is a noncompetitive inhibitor at both the alpha7 and alpha4beta2 nAChR. In contrast, BCl causes a parallel shift in the ACh dose-response curve at the alpha7 nAChR suggesting competitive inhibition. Ketamine causes both voltage-dependent and use-dependent inhibition, only in the alpha4beta2 nAChR. 4. Since alpha7 nAChRs are likely to be inhibited during clinical use of Ketalar, the actions of ketamine and BCl on this receptor subtype may play a role in the profound analgesia, amnesia, immobility and/or autonomic modulation produced by this anaesthetic.

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Preservative-free ketamine

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Editor—We were delighted to read the review article on 'Caudal additives in children—solutions or problems?'.[1] We have used preservative-free caudal ketamine for over 330 general surgical, urological and orthopaedic paediatric cases in Chelmsford since 1998, providing excellent, prolonged analgesia with no untoward effects.

In the authors' summary paragraph they conclude that 'a combination of ketamine 0.5 mg kg^{-1} and bupivacaine is even more effective [than clonidine 1 μg kg^{-1}], providing analgesia for up to 12 h'. These additives, they concluded, had superseded the use of caudal opioids and we wholeheartedly concur with these findings.

We were rather disappointed to then read: 'however, further study and the introduction of ketamine into mainstream clinical practice is limited by the difficulties in obtaining preservative-free ketamine and ongoing concerns about

potential neurotoxicity'. They also state that 'the use of caudal additives for day-care anaesthesia is controversial and at present their routine use cannot be recommended'. We have obtained preservative-free ketamine 10 mg ml^{-1} (50 mg ampoules) on a named-patient basis since 1998 from Ketamin Curamed (Ketamine—Curamed Pharma GmbH, Postfach 41 02 29, D-76202 Karlsruhe, Germany).

The authors question the safety of epidural ketamine and quote a paper by Stotz.[2] This paper reported a case of a 72-yr-old woman who developed isolated lymphocytic vasculitis of the spinal cord and leptomeninges after a 7 day infusion of ketamine, clonidine, morphine and bupivacaine, although she showed no signs of neurological deficit. The ketamine used was the commercially available ketamine with benzethonium preservative. The patient had an intrathecal catheter *in situ* for 18 days, initially with morphine 0.12 mg ml^{-1} and bupivacaine 0.25% given at 2–2.5 ml h^{-1}. The dose was then increased to 3–3.5 ml h^{-1} and the morphine increased to 0.3 mg ml^{-1}. During this time, she developed signs of meningitis. Stotz and colleagues concluded that 'the changes may be related to the preservative benzethonium chloride or the toxicity of the mixture itself'.[2] With regard to the use of caudal additives for day-care anaesthesia, we are at a loss to understand why the authors think that the addition of preservative-free ketamine to caudal bupivacaine should be controversial. Is it their worry of neurotoxicity or some other long-term side-effect that concerns them?

We feel that the addition of preservative-free ketamine to caudal bupivacaine is not only a good analgesic but should be the method of choice in this type of paediatric case.

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Editor—We are pleased that Drs Huddy and Kiff enjoyed our recent review,[1] and we thank you for the opportunity to reply. With regard to the availability of preservative-free ketamine, we are glad to read the authors' ease in obtaining this, albeit on a named-patient basis. This necessarily cumbersome process represents a practical barrier to its more widespread acceptance. As was reported recently,[3] preservative-free ketamine is now available in this country and therefore no longer has to be imported directly from Germany. This, we trust, will increase the frequency with which it is used.

We were delighted to hear of yet more evidence, albeit anecdotal, of Drs Huddy and Kiffs' positive experiences with the drug as a caudal additive in children and would encourage them to formally report their data to add to the growing, yet still small, body of clinical evidence to support its use.

As regards neurotoxicity, Huddy and Kiff are quite correct in drawing attention to the equivocal aetiology of the only human case report of neurotoxicity associated with epidural ketamine. However, as stated in our review,[1] there is animal data of the vacuolation of posterior root ganglia attributable to ketamine, admittedly at high doses.

With regard to the use of caudal additives for day-case anaesthesia, we stand by our original statement and maintain that, at present, their routine use cannot be recommended. The reason for this relates to the potential problems that may arise after discharge as a result of prolonged sensory and motor block, in particular block of thermal sensibility.[4] While these problems might also occur with the use of plain bupivacaine, the use of additives such as clonidine and ketamine increases the risk.

We therefore feel it is worth exercising caution rather that advocating its widespread use while the body of clinical evidence tips ever more in favour of caudal ketamine.

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